UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,990	09/29/2006	Manuel Worcel	0102258.00375US2	4629

24395 7590 09/17/2009

WILMERHALE/DC
1875 PENNSYLVANIA AVE., NW
WASHINGTON, DC 20006

EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
09/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

teresa.carvalho@wilmerhale.com
michael.mathewson@wilmerhale.com
sharon.matthews@wilmerhale.com

Office Action Summary	Application No.	Applicant(s)	
	10/594,990	WORCEL, MANUEL	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5 and 21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on July 20, 2009.

Status of Claims

Cancellation of claim 4, amendment of claims 1 and 5, and addition of claims 21-25 is acknowledged.

Claims 1, 5 and 21-25 are currently pending and are the subject of this office action.

Claims 1, 5 and 21-25 are currently under examination.

Priority

The present application is a 371 of PCT/US05/107384 filed on 03/31/2005, and claims benefit of provisional application No. 60/557,700 filed on 03/31/2004.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103 (new Rejection not Necessitated by Amendment)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 5 and 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler et. al. (US 6,472,390, cited in prior office action) in view of Adams et. al.(US 6,747,063, cited in prior office action), and over Goodman (US 6,087,398, cited in prior office action) in view of Loscalzo (US 6,635,273).

Claim 1 recites a method for treating sickle cell anemia in a patient in need thereof comprising administering to a patient in need thereof a therapeutically effective

amount of N-hydroxy-L-arginine, isosorbide dinitrate, isosorbide mononitrate or a mixture of two or more thereof, and at least one hydralazline compound or a pharmaceutically acceptable salt thereof.

Claim 5 further limits claim 1, wherein the hydralazline compound is hydralazline hydrochloride.

Claim 21 further limits claim 1, wherein the hydralazline compound is selected from the group consisting of: hydralazline, etc.

For claims 1, 5 and 21, Stamler teaches a method of treating sickle cell anemia comprising the administration of an NO (Nitric Oxide) donor (see claims 10, 18 and 21).

Stamler does not teach the use of N-hydroxy-L-arginine, isosorbide dinitrate, isosorbide mononitrate or a mixture of two or more thereof for the treatment of sickle cell anemia. However, Adams teaches that N-hydroxy-L-arginine, isosorbide dinitrate, and isosorbide mononitrate are NO (Nitric Oxide) donors (see column 3, lines 43-54).

Neither Stamler nor Adams teach the treatment of sickle cell anemia with hydralazines or pharmaceutically acceptable salts thereof. However, Goodman teaches the treatment of sickle cell anemia with antioxidants (i.e. reducing agents) (see abstract, claims 1-3) and Loscalzo teaches that hydralazine and hydralazine hydrochloride are known antioxidants (see column 12, lines 34-54).

At the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to treat sickle cell anemia combining two compositions (a NO donor and an antioxidant) each of which is taught by the prior art to be useful for the

same purpose (treating sickle cell anemia), in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). And since Adams teaches that N-hydroxy-L-arginine, isosorbide dinitrate, and isosorbide mononitrate are NO (Nitric Oxide) donors, and since Loscalzo teaches that hydralazine and hydralazine hydrochloride are known antioxidants, at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (any NO donor) for another (N-hydroxy-L-arginine, isosorbide dinitrate, and isosorbide mononitrate) and any antioxidant for another (hydralazine and hydralazine hydrochloride) with an expectation of success, since the prior art establishes that they function in similar manner, thus resulting in the practice of claims 1, 5 and 21, with a reasonable expectation of success.

Claim 22 recites a method for treating thalassemia in a patient in need thereof comprising administering to a patient in need thereof a therapeutically effective amount of N-hydroxy-L-arginine, isosorbide dinitrate, isosorbide mononitrate or a mixture of two or more thereof, and at least one antioxidant

Claim 23 further limits claim 22, wherein the antioxidant is selected from the group consisting of: hydralazine among others.

Claim 24 further limits claim 22, wherein the antioxidant is a hydralazine compound.

Claim 25 further limits claim 24, wherein the hydralazine compound is hydralazine hydrochloride.

For claims 22-25, Stamler teaches a method of treating thalassemia comprising the administration of an NO (Nitric Oxide) donor (see claims 10, 18 and 21).

Stamler does not teach the use of N-hydroxy-L-arginine, isosorbide dinitrate, isosorbide mononitrate or a mixture of two or more thereof for the treatment of sickle cell anemia. However, Adams teaches that N-hydroxy-L-arginine, isosorbide dinitrate, and isosorbide mononitrate are NO (Nitric Oxide) donors (see column 3, lines 43-54).

Neither Stamler nor Adams teach the treatment thalassemia with antioxidants or more specifically with hydralazines. However, Goodman teaches the treatment of sickle cell anemia with antioxidants (i.e. reducing agents) (see abstract, claims 1-3) and Loscalzo teaches that hydralazine and hydralazine hydrochloride are known antioxidants (see column 12, lines 34-54).

At the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to treat thalassemia combining two compositions (a NO donor and an antioxidant) each of which is taught by the prior art to be useful for the same purpose (treating thalassemia), in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). And since Adams teaches that N-hydroxy-L-arginine, isosorbide dinitrate, and isosorbide mononitrate are NO (Nitric Oxide) donors, and since Loscalzo teaches that hydralazine and hydralazine hydrochloride are

known antioxidants, at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (any NO donor) for another (N-hydroxy-L-arginine, isosorbide dinitrate, and isosorbide mononitrate) and any antioxidant for another (hydralazine and hydralazine hydrochloride) with an expectation of success, since the prior art establishes that they function in similar manner, thus resulting in the practice of claims 22-25, with a reasonable expectation of success.

Conclusion

No claims are allowed.

.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
August 28, 2009.

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612